

### Remarks

Claims 1-11 and 17-21 are pending in the application. Claims 18-21 are new. New Claims 18-20 are directed to methods of treating or preventing thrombosis or diseases accompanying thrombus using the pharmaceutical composition of Claim 17. Support in the specification for new Claims 18-20 can be found, for example, on page 25, line 3 through page 26, line 4. New Claim 21 is directed to a method of inhibiting or preventing platelet aggregation using the pharmaceutical composition of Claim 17. Support for new Claim 21 can be found in the specification, for example, on page 2, lines 19-20 and on page 5, lines 13-23.

The Applicants acknowledge the objection to Claim 2 based on the term “general”. In accordance with the Examiner’s helpful suggestion, the term has been deleted.

The Applicants acknowledge the rejection of Claims 1-11 and 17 based on the doctrine of obviousness-type double patenting over U.S. Pat. No. 6,407,096 (“Ohtake”). As discussed in the background section of the present application, Ohtake describes benzomorpholine derivatives having an inhibitory effect on platelet aggregation. However, Ohtake does not describe or suggest that the compounds specifically claimed in the present application, *i.e.*, those having the amide structure set forth in independent claims 1 and 17, would have a dramatically increased and advantageous effect on platelet aggregation over the broad genus of compounds claimed in Ohtake. The marked increase in activity of this species, as described and claimed in this application, represent an unexpected and surprising result over the genus of Ohtake.

The Applicants thank the Examiner for the courtesy shown during the telephonic interviews on November 17 and November 28, 2005. The teachings of Ohtake and the unexpected results exhibited by the particular species of compounds of this invention were discussed. These topics will be discussed below in more detail.

The Applicants acknowledge that the subject matter claimed in Ohtake may overlap the subject matter presently claimed when A<sup>3</sup>, R<sup>1</sup>, R<sup>3</sup>, A<sup>1</sup>, A<sup>2</sup> and A<sup>4</sup> are all assumed to be specific groups. Therefore, this is a case of “domination” controlled by the decision of *In re Kaplan*, 229 USPQ 678 (Fed. Cir. 1986). A case of domination occurs when an earlier patent includes broad or generic claims which read on an invention defined by a later patent (or application) having narrower or more specific claims. Such a situation does not, per se, rise to the level of double patenting. *In re Kaplan* at 681. Because the claims of the later patent (in this case, the present application) are narrower than the earlier patent, they are not “the same” invention. The relevant inquiry then is

whether the invention claimed in the later patent is a mere variation of the earlier claimed invention that would have been obvious to those of ordinary skill in the art. *Id.* at 682. Thus, an obviousness-type double patenting rejection in this circumstance can only stand if there is clear evidence to establish that the variation would have been obvious. *In re Kaplan* at 683.

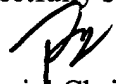
Ohtake discloses a broad range of compounds, including 41 specific examples. However, Ohtake includes no suggestion or motivation to select a species from within that broad range in accordance with Claim 1 in the instant application, characterized by the presence of an amide group. Further, Ohtake includes no hint, let alone data, that would suggest to the skilled artisan that the species presently claimed would have any effect on platelet aggregation that would be better than that described for the genus generally. Ohtake provides platelet aggregation inhibiting action IC<sub>50</sub> data in Tables 1 and 2 (Examples 42 and 43) for various exemplary compounds. Table 2 shows the platelet aggregation inhibiting action experimentally determined using ADP as a platelet aggregation inducer. These IC<sub>50</sub> values range from 0.95 to 16  $\mu$ M. Ohtake is silent as to the ability of any compound or species to achieve 50% aggregation inhibition at concentrations lower than about 1  $\mu$ M. Because Ohtake fails to appreciate that the compounds now specifically claimed could have such activity at lower concentrations, and because Ohtake fails to describe any other advantage of using the particular species, Ohtake includes no suggestion to specifically select compounds according to the formula of Claims 1 and 17.

In sharp contrast to the prevailing wisdom in the art at the time this invention was made, the present inventors have unexpectedly found that the particular species according to the formula set forth in Claims 1 and 17 has significantly increased platelet aggregation inhibitory effect over that of the Ohtake genus generally (IC<sub>50</sub> values of about 1  $\mu$ M or more). Table 34 on page 57 of the present specification clearly shows these unexpected results, using ADP as an aggregation inducer and conditions otherwise comparable to Ohtake. As shown in Table 34, compounds within the species of Claims 1 and 17 have platelet aggregation inhibitory effect IC<sub>50</sub> values ranging from 5.3 to 31 nM. This IC<sub>50</sub> data is in sharp contrast to the  $\mu$ M ranges set forth in Ohtake, and establishes that the species of this invention exhibits increased activity of about two orders of magnitude. For example, as shown in Table 34 of the specification and Table 2 of Ohtake, the compound of Example 21 of Ohtake has a platelet aggregation inhibiting action IC<sub>50</sub> of 1800 nM (*i.e.*, 1.8  $\mu$ M). Thus, the species defined by the claims of this application exhibit greatly improved platelet aggregation inhibiting activity over the broad genus described and claimed in Ohtake.

It is respectfully submitted that the platelet aggregation inhibitory effect exhibited by the species of this invention represents a surprising and unexpected effect over the genus of compounds claimed in Ohtake. Because the selection of the compounds presently claimed is not suggested in Ohtake, one skilled in the art would not have been motivated to select the species defined by the formula set forth in Claims 1 and 17. Moreover, the unexpected results shown in Table 34 of the specification represent compelling objective evidence of non-obviousness. Therefore, it is respectfully submitted that the species presently claimed is not a mere obvious variation of the genus of Ohtake, and that the present claims are patentable thereover. For these reasons, it is respectfully requested that the present rejection be reconsidered and withdrawn.

In light of the foregoing, the Applicants respectfully submit that the entire application is now in condition for allowance, which is respectfully requested. If the Examiner believes that further minor amendments or corrections as to matters of form would advance the application, the Examiner is invited to telephone the Applicants' undersigned attorney.

Respectfully submitted,



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